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ACUTE OBSTRUCTION
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THE SUPRARENAL VENA CAVA

by

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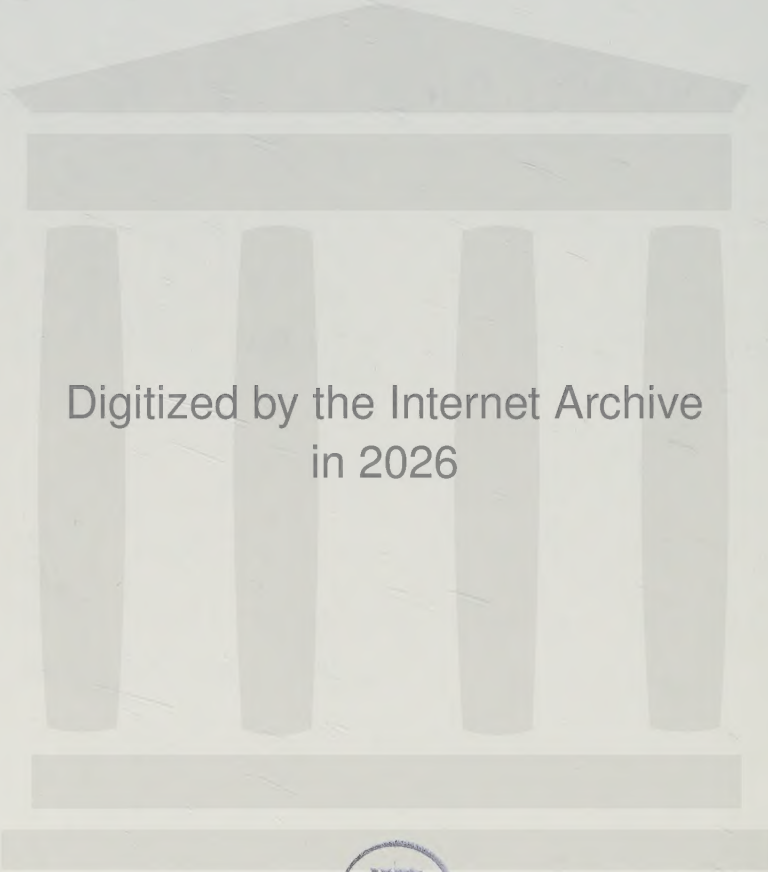
An experimental study in rats and rabbits

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This thesis is based on the following papers:

- I. Bengmark, S. & Olsson, A.M.: Acute obstruction of the suprarenal vena cava in the rat. Mortality, urine production, creatinine, urea nitrogen, osmolality and protein in urine.
- II. Bengmark, S. & Olsson, A.M.: Acute obstruction of the suprarenal vena cava in the rat. Changes in electrolytes, urea, creatinine, and acid-base-balance.
- III. Bengmark, S., Olsson, A.M. & Schröder, R.: Acid-base, electrolyte, urea and creatinine changes following nephrectomy, adrenalectomy and infrarenal vena cava ligation in rats.
- IV. Olin, T. & Olsson, A.M.: Renal blood flow and function following suprarenal ligation of the inferior vena cava. An experimental study in rabbit.
- V. Du Rietz, B. & Olsson, A.M.: Renal changes in rats after ligation of the inferior vena cava above the renal veins.
- VI. Olin, T. & Olsson, A.M.: Rubidium redistribution after suprarenal caval ligation in the rat.

These papers are referred to in the text by their Roman numerals.

ACUTE OBSTRUCTION OF THE SUPRARENAL VENA CAVA

Introduction

For several reasons, the past three decades have seen a growing interest in acute suprarenal vena cava ligation (SRVCL). Occasionally, renal tumours, hypernephromas, and nephroblastomas invade the vena cava. In hepatic tumour surgery, it is sometimes of great advantage to close the vena cava, temporarily or permanently.

There also exists a rare group of primary tumours of the vena cava classified as leiomyosarcoma, leiomyoma, endothelioma, and endochondroma. Only about a dozen cases are reported, their clinical malignancy being low grade, and they seldom metastasize.

Accidental injuries also occur.

In the literature on acute obstruction of the suprarenal vena cava, many authors confuse suprarenal and infrarenal vena cava ligation, (IRVCL), vena cava thrombosis (both infra- and suprarenal), ligation of renal veins, and thrombosis of renal veins. There are so many pathophysiological differences between these concepts, especially the effect on renal function, general circulation, and peripheral veins, that it is necessary to study and discuss each topic separately. So far, there is no acceptable substitute for the caval vein (24). The question sometimes arises whether a resection or ligation of the suprarenal vena cava is possible, and if so, what the consequences will be. Although a high mortality in experimental animals — mainly dogs — after suprarenal ligation is well known, nobody has indicated the cause of death.

Scope of the investigation

The objective of the present study was to clarify:

1. To what extent suprarenal vena cava ligation influences the general circulation and renal function,
2. How deep and how long this impairment is,
3. Whether one part of the kidney is affected more than others,
4. Whether any of suggested causes of death could be excluded,
5. Whether it is possible to prove any cause of death.

A survey of literature

The first published experiment with suprarenal vena cava ligation was made by Richard Lower 1669 (44) who in his "Tractatus de corde" states that he ligated the inferior vena cava of a dog a short distance below the heart. Death occurred a few hours later.

Schouttellen 1827 (66) ligated the inferior vena cava of an animal and attributed the fatal result to cardiac insufficiency. Purpura 1899 (56) performed acute ligation of inferior vena cava in 25 dogs at varying locations between the hepatic veins and the iliac bifurcation. There were 18 deaths and 7 survivors. Among the survivors, one had the ligature below the renal veins, five above the renal veins, and one at or above the adrenal veins.

Gosset and Lecene 1904 (32) stated that death always resulted from a ligation of the inferior vena cava above the renal veins in dogs. Leotta 1907 (41) mentioned similar experimental results. Polkey 1929 (55) found that only one of five dogs survived suprarenal vena cava ligation. Death occurred 12 - 72 hours after the ligation.

Montemartini 1934 (47) published data confirming almost universal fatality in dogs resulting from ligation of the inferior vena cava above the renal veins.

Addis and Lew 1939 (2) ligated suprarenal vena cava in rats of different ages. They found a rising mortality with age (90 % in the oldest rats) and they proposed uremia as cause of death. Whittenberger and Huggins 1940 (75) ligated the suprarenal vena cava on two dogs. Both died 5 and 10 hours, respectively, after the ligation.

Ripstein et al 1952 (59) operated 42 dogs with ligation of the vena cava above both adrenal veins. 45 % (18 dogs) survived. 24 dogs died, 10 during the first postoperative 12 hours in a shock-like state, 5 died during the period 12 to 24 hours, and 9 between 24 and 48 hours. Urine output ceased and blood urea nitrogen began to rise, reaching a peak in 72 hours. In those animals that survived, diuresis occurred at that time. Blood urea nitrogen reached normal values in 8 to 10 days. Other blood chemistry values were normal except cholesterol, which rose until the 4th day and then declined to normal values by the 8th day. The authors stressed that death could not be due to renal failure alone, as it is estab-

lished that death due to uremia after bilateral nephrectomy occurs in 8 to 10 days in dog.

Lejeune-Ledant 1957 (40) ligated suprarenal vena cava above the both adrenal veins in 12 dogs; 10 survived. He encountered a shorter period of nephropathy in his surviving animals with elevated BUN, haematuria for some days, and a trace of albuminuria. In the two fatalities, an autopsy revealed an inadvertent occlusion of the azygos vein by the ligature.

Nesbit and Wear 1961 (49) operated 5 dogs with suprarenal caval ligation. Four of them died in a shock-like state within 36 hours after the operation. Autopsy findings included marked congestion and cyanosis of the kidneys, distension of the veins below the ligature, and a moderate amount of haemorrhage into the perirenal and retroperitoneal tissue. The survivor went through a transitory phase of renal failure characterized by oliguria and azotemia. The urinary output was less than 300 cc for each of the first two days and then rose. The blood urea nitrogen rose to 62 mg % on the second postoperative day. There was no significant change in the serum electrolytes during this period.

Bejan and Cohn 1911 (9) attributed major importance to the adrenal veins in the collateral venous circulation because four animals subjected to a ligature above the adrenal veins died, whereas six of eight animals subjected to a ligature below the right adrenal, but above the left adrenal and both renal veins, survived.

Roy-Camille and Leger 1963 (60) operated 4 dogs with suprarenal vena cava ligature. One survived. They proposed the stasis on the adrenal glands as a cause of adrenal insufficiency with shock and death.

Grote 1964 (33) stated that ligation and resection of vena cava between the renal and hepatic veins is not compatible with life: he demonstrated a two-stage procedure which was successful.

Beilin et al 1971 (8) showed that if the dog had a functioning femoral-to-jugular vein shunt for 48 hours after a suprarenal ligation, they had a survival of 3/5 dogs — one died in aspiration and one in peritonitis — compared with a survival of 2/10 without shunt.

A procedure somewhat resembling suprarenal vena cava ligation is an oblique inter-renal ligation of inferior vena cava. Leotta 1907 (41) made the report of this technique. He had a 33 % mortality in dogs. The same year, Offergelt (51) showed even better results on cats, dogs, and rabbits. Whittenberger and Huggins 1940 (75) continued to study oblique inter-renal ligation. They found that the kidney below the ligature went through a phase of renal failure which resolved in 4 of 5 cases in three to six weeks. Thereafter, the dogs tolerated a ligature placed across the inferior vena cava above both adrenal veins.

So far, only 8 cases of humans with suprarenal vena cava ligation are reported.

1. Delbet 1923 (transitory polyuria) (23),
2. Ripstein and Miller 1949 (anuria, haemodialysis) (58),
3. Bolot 1954 (transitory oliguria) (12),
4. Petkovic 1957 (transitory renal failure) (53),
5. Fitzsimons and Garvey 1959 (left splenorenal shunt, postoperative temporary renal failure) (27),
6. Huber 1961 (a 6 year old girl with Wilms tumour - no postoperative renal problems) (64),
7. Mehta 1968 (transient oliguria) (45),
8. Gazzaniga and Colodny 1972 (8 1/2 year old girl with no postoperative renal depression) (30).

There are also reports of suprarenal vena cava ligation preceded by a chronic obstruction of the caval vein (16).

In five of these, suprarenal vena cava was ligated at a right nephrectomy; in all of them a great loss of blood preceded the ligation. All cases, except those of Huber and Gazzaniga together with Colodny, which were children, went through a transitory phase with renal failure and in one case (Ripstein and Miller) the patient had a haemodialysis before recovery. It should be observed that hitherto no report of suprarenal vena cava ligation in humans with fatal outcome is reported. Our interpretation is that a fatal outcome to an inadvertent injury is not reported.

It is also worthy of note that Sapirstein and Reininger (63) state an improvement in survival of dogs if right nephrectomy is done two weeks before suprarenal vena cava ligation. The rationale underlying this is to diminish the load on the developing collaterals.

Lespinasse 1947 (42) performed simultaneous ligation of the inferior vena cava above and below the renal veins, both with and without an associated right nephrectomy, and found that one cat, one dog, one monkey, ten rabbits, and 28 out of 30 rats survived. He contented that the high survival rate was due to a reduction in the degree of passive congestion in the kidney.

If the pathophysiology after SRVCL is confused, the histological lesions of the kidney are no less unsettled. The renal lesions described are discrete, but most are rather later after the SRVCL (43, 59, 71, 68, 73, 74) Besides, only isolated survivors are examined.

Critical evaluation of the literature

From the dispersed dates of the available literature, we find a rather high and early mortality after SRVCL, although its ground is quite obscure, but the development of collaterals is essential. Most authors have limited their studies to the description of mortality rate, venous collaterals, isolated BUN values, and some other parameters that could be estimated or seemed to be of interest. But the effect on the general circulation, the blood flow in the stasied organs, and the kidney function are still uninvestigated. Studies are lacking that systematically tackle each question separately and thereby plot the pathophysiology after SRVCL.

MATERIAL AND METHODS

Experimental animals

Choice of experimental animals

In paper I, II, III, V, and VI, we chose male Sprague-Dawley rats because we wanted a standardized animal with known weight and age, easy to handle, and in good supply. Also the cost of a great number of animals must be moderate. In paper IV, we found that the rabbit would be ideal as we wanted a somewhat bigger animal in which accurate studies of blood flow and renal function could be made.

We used in reports I, II, III, V, and VI, male Sprague-Dawley rats of different ages and in report IV young rabbits weighing 1.6 - 2.5 kg. The rats were pre- and postoperatively fed with water and food ad libitum. Pellets (Astra-Evos) containing crude protein 21.5-23.5

%, crude fat 3.5 - 4.5 %, and 2.5 - 3.5 % vegetable fibres. It also contained calcium 1.1 - 1.4 %, potassium 0.4 %, phosphorus 0.8 - 1.0 %, common salt 0.3 - 0.4 %, ash 7.5 %, water 11 %, vitamins, and trace elements. The rabbits also had water and food ad libitum pre- and postoperatively (Astra-Ewos). The content of the pellets was crude protein 20 - 22 %, crude fat 4.5 - 5.5 %, vegetable fibres 11.0 - 13.0 %. Also calcium 0.7 - 1.0 %, phosphorus 0.5 - 0.7 %, common salt 0.2 - 0.3 %, ash 8.0 %, water 11 %, vitamins, and trace elements.

Experimental technique

The rats were anaesthetized with ether, whereafter a midline incision was made to avoid destroying any vessels of the abdominal wall. The vena cava was dissected free, and a ligature was put around it and tied in an infrarenal or suprarenal position. In the rats going to nephrectomy, the same incision was made, the kidneys were dissected free, and the renal stalk was tied en bloc with a silk ligature. The abdomen was closed in one layer with separate sutures. When the blood samples were taken, the animals were given a slight ether anaesthesia and the same approach to the abdomen was made. The aorta was punctured directly, and the animals were exsanguinated. The rats in the histological study V were also anaesthetized when the kidneys were taken out. Before that, the renal stalk had been ligated to get an idea in the histological picture of the grade of stasis. Each kidney was then weighed separately before and after fixation in 10 % formalin.

The rabbits were anaesthetized with pentobarbitone sodium intravenously (Mebumalnatium, ACO, Sweden). Also here a midline incision was made to save the vessels of the abdominal wall. The inferior vena cava was dissected free just above the right renal vein, and a silk ligature was placed and tied there causing an acute obstruction of the vena cava. The abdominal wall was closed with separate sutures in two layers. The blood loss during the operative procedures was minimum in both the rats and the rabbits.

Just after the vena cava ligation was performed, the distal veins were filled and stased. In those animals exposed to suprarenal vena cava ligation, the kidneys immediately after ligation assumed a bluish colour and a harder consistency. The venous collaterals from the lower part of the body were also better visualized.

Before the rabbits were investigated, they were given a slight intravenous pentobarbitone anaesthesia combined with local anaesthesia (Carbocain 1 %, Bofors, Sweden) in the neck and groins, where the catheters were introduced. This form of anaesthesia does not affect the rabbits' circulation (52). In the experimental studies in rabbits, the renal artery was catheterized from the femoral artery (1) with a thin radiopaque catheter (OPP 60, Portex, England, OD/ID = 1.22/0.75 mm). The corresponding renal vein was catheterized from the femoral vein by a soft radiopaque catheter (RO I, Portex, England, OD/ID = 1.45/0.7 mm) with side holes close to the tip. The arterial blood pressure was monitored by a catheter in the right carotid artery and an electromanometer (Elema-Schönander). The central venous pressure was measured by a catheter introduced into the right jugular vein. The immediate effect of the acute occlusion of the supra-renal vena cava was studied by a balloon technique. A balloon catheter (Swan-Ganz Flow directed catheter 5 F, Edwards Laboratories, USA) was introduced into the superficial right jugular vein and placed in the inferior vena cava cranial to the entrance of the right renal vein. The inflation of the balloon completely occluded the lumen of the caval vein.

Dye-dilution method

To measure the renal blood flow (RBF) for one kidney (25), the catheter in the renal artery was filled with indocyanine green (Cardio green, Hynson, Westcott & Dunning Inc., USA) and 0.1 ml was rapidly injected. The cardiac output (CO) was measured by injecting 1 ml of the dye with the same technique through the central venous catheter. The sampling was made from the catheter in the renal vein and carotid artery, respectively. The sampling catheters were connected to a moto-driven suction syringe. A small amount of blood was aspirated at a constant rate through a densitometer, and a continuous registration of the dye concentration could be effected on the potentiometer recorder. The area of the curve was calculated by comparing the weight of the excised curve (M gram) with the weight of 100 square units of the same paper (m_{100} gram).

The calculations were performed according to the formula:

$$\text{CO or RBF} = \frac{q \cdot D \cdot m_{100}}{M} \cdot 60$$

where CO = cardiac output (ml/min),
RBF = renal blood flow (ml/min),

q = amount of injected dye (ml) ,

D = deflection (cm) on the potentiometer recorder when it was calibrated with 0.1 ml of dye in 10.0 ml of blood.

Extraction and clearance investigated with ^{51}Cr -EDTA and ^{125}I -Hippuran

The radiochemicals ^{51}Cr -EDTA and ^{125}I -Hippuran mixed in isotonic glucose, were given as a priming dose intravenously, 10 ml in four minutes followed by a slow intravenous infusion 10 ml in 36 minutes. Arterial blood and renal vein blood were withdrawn simultaneously and analysed in a dual well-crystal channel scintillation detector (Selektronik, Denmark). The detector can separate the radiation from ^{51}Cr -EDTA and ^{125}I -Hippuran. The clearance value (ml/min) of ^{51}Cr -EDTA was calculated by the formula:

$$\text{Cl} = \text{RBF} \cdot E \left(1 - \frac{\text{Hct}}{100} \right)$$

RBF = renal blood flow (ml/min) ,

E = extraction ratio of EDTA ,

Hct = hematocrit (%) measured by a micromethod (Minor , MSE , England) .

Chemical analytic methods

Sodium and potassium in plasma and urine were determined by flamephotometry. The protein concentration in urine was analysed by the biuret method. Creatinine and Urea-N concentrations were determined by autoanalytical methods (Technicon).

Osmolality was estimated by freezing point depression. The routine chemical laboratory of the hospital was used for these analyses.

Standard bicarbonate, base excess, pH, P_{CO_2} , and P_{O_2} were determined according to Sigaard-Andersen (69).

Lactate was determined by the Biochemica Test Combination technique (Boehringer, Mannheim, Germany).

⁸⁶Rubidium estimates

The content of ⁸⁶Rb in aortic blood, heart muscle, muscle of thigh and shoulder, and kidney and liver was measured in a scintillator (Selektronik, Denmark). The time was 400 seconds for both background and specimen. The radioactivity was expressed in counts per gram wet weight (c/g).

Short summaries of the reports

I. The suprarenal vena cava was ligated on male Sprague-Dawley rats of different ages. The mortality in rats less than 45 days of age was considerably less than in rats more than 95 days. The young ones died within the first three days, whereas the period for the older ones lasted for up to one week. In those animals that died, a marked oliguria, proteinuria, and a concentration defect developed after operation. In those that recovered, the impairment of the renal function was less pronounced. In the older surviving animals, a low urinary osmolality was still seen at the end of the observation period, 40 days after the operation.

II. The suprarenal vena cava was ligated on male Sprague-Dawley rats with a mean weight of 180 g, i.e. about 45 days of age. Lactate, acid-base, serum urea, and creatinine, as well as electrolytes, were measured, especially often during the first two days and were followed until the 16th day. There was an immediate and dramatic rise of potassium with a mean maximum after 12 hours, 8.3 mE/l and single values up to 10.0 mE/l were measured. The normal level was reached after 4 days. The changes in serum sodium was much less; the curve resembled the inverted potassium curve. There was also a rise in serum urea and creatinine with its apex after 24 - 48 hours. A slight acidosis was noted with slightly elevated lactic acid values during the first 8 hours after SRVCL. In another group with different ages, the electrolytes in urine were studied. Low values were found during the first week and normalization occurred faster in the young ones.

III. Three groups of male Sprague-Dawley rats with a mean weight of 180 g were operated:

Group A: ligation of infrarenal vena cava ,
Group B: bilateral nephrectomy ,
Group C: bilateral adrenalectomy .

At short intervals from 3 to 48 hours after the operation , the animals were exsanguinated by puncture of the aorta , and acid-base , electrolytes , urea nitrogen , and creatinine were studied .

The adrenalectomized rats had a slight constant hyperkalaemia as did the infrarenal ligated ones , but only during the first 9 hours postoperatively . The nephrectomized animals had a biphasic serum potassium curve with an early maximum after 12 hours with a mean of 7.6 mE/l , combined with a quick rise of urea nitrogen . Between 12 and 24 hours postoperatively , the urea nitrogen was rather constant , but serum potassium dropped to a mean value of 5.9 mE/l . More than 24 hours after nephrectomy the potassium and urea nitrogen rose again together with the appearance of a metabolic acidosis . The creatinine rose constantly during the study .

IV. The renal blood flow and function were studied after acute ligation of the inferior vena cava cranial to the right renal veins in rabbits . The function , as measured by the extraction of EDTA and Hippuran , diminished and often reached the lowest values at the fourth day . After the fourth day , the function returned to normal values or mortal renal failure developed . The cardiac output and renal blood flow diminished immediately at ligation , then increased towards normal values which could occur rather early - four days - but usually took 16 days . The pressure in the renal vein increased four fold after the acute occlusion and fell during the study to nearly normal values after one month . The low glomerular filtration rate is roentgenologically revealed by low density of the urogram and a weak nephrographic phase of the cortex during the renal angiography . Segmental drainage with several "water sheds" developed in the inferior caval vein , whose diameter diminished during the observation time to $\frac{4.5 - 5}{4}$ mm at the end of the study . The

most important drainage of the renal veins was by way of the supra-renalolumbar veins which increased somewhat in calibre .

V. To study the renal morphological changes after SRVCL, three groups of male Sprague-Dawley rats were used.

Group I, weight 175 - 210 g, age about 45 days,
Group II, weight 300 - 350 g, age about 65 days,
Group III, weight 400 - 580 g, age above 120 days.

Laparotomy was performed under ether anaesthesia by a midline incision. The vena cava was dissected free and ligated with a silk tie just above the renal veins. In sham-operated animals only the dissection was performed.

The postoperative mortality was 35, 55 and 65 per cent, respectively, in the three groups. Two months after the SRVCL, the most essential collaterals were suprarenolumbar veins, lumbarintercostal veins, and veins overbridging the caval ligature.

The acute renal injury produced by the caval obstruction was manifested by degeneration and necrosis of the tubules, most conspicuously in the inner stripe of the outer medulla and the adjacent inner medulla, hyaline and granular casts, medullary congestion, and minor though varying degrees of cortical lesions. Glomerular changes were minimum. Two to three days after caval ligation epithelial regeneration originating from residual surviving tubular cells was prominent. Fibroblasts were seen proliferating around and into necrotic and disrupted nephrons. At the same time, dilation of tubules was marked in the older rats. The regeneration cells had relined most of the denuded tubules within one week. The kidneys regained an essentially normal structure one to two months after the ligation. The younger rats showed somewhat less initial renal damage and recovered earlier with only a slight persisting interstitial fibrosis. The acute lesions were more pronounced in the older rats, which also recovered at a slower pace and with somewhat more sequelae. Most of the spontaneously dying animals showed extensive renal lesions, in many cases also medullary infarctions.

VI. After injection of ^{86}Rb in the tail vein of male Sprague-Dawley rats, there was a redistribution during the first 12 hours followed by a steady state. In another group, a SRVCL was performed 15 hours after the ^{86}Rb injection. This caused almost half of Rb-content of the kidney to disappear. Also the thigh musculature lost

some Rb, whereas the shoulder musculature, and still more the liver, gained Rb at the same time.

DISCUSSION

Since J. Hall Pleasants published his classical report about obstruction of the inferior vena cava 1911 (54), only a few more clinical reviews have been written (46,13). 1961 Nesbit and Wear (49) not only made a summary of literature about suprarenal vena cava ligation in man and animals, but also presented their own experimental data from five dogs. Scharfetter 1967 (64) published a detailed review called "Ligatur der unteren Hohlvene zwischen den Mündungen der Lebervenen und der Nierenvenen", i.e. suprarenal vena cava ligation. He summed up that ligation of suprarenal vena cava did not always lead to death — and nobody has ever been able to identify the cause or causes either in man or in animals.

Although there are several proposals: shock, uremia, and adrenal insufficiency (2,7,59,71,60) nobody has ever been successful with shock-therapy or corticosteroids (36,64,8). The only successful procedure is reported by Beilin et al 1971 (8). They used a femoral to jugular vein bypass on dogs for 48 hours. After the shunt was opened there was no longer an acute obstruction of the suprarenal vena cava.

In both dogs and rats, the main mortality is restricted to the first three postoperative days. This has led most authors to reject the proposal of an acute uremia as a cause of death.

Andreasson and Watson (6) found that if vena cava inferior was clamped in the thorax, the blood flow to heart and brain was sufficient for at least 35 minutes, through a compensatory five-fold increase of azygos flow. Similar results were obtained by Cohen and Lillehei (19). Obviously the collateral flow can be enormously increased after a caval vein occlusion.

Farber et al (26) made acute balloon occlusion of the suprarenal vena cava for 30 minutes on patients in order to study the renal influence. They found that the systemic artery pressure fell slightly and that the renal plasma flow and glomerular filtration rate decreased 15 to 25 per cent. Their results are consistent with ours (paper IV), although in rabbits we found greater diminishing of renal blood flow, i.e. more than 50 % reduction and a fall of the central blood pressure of about 25 %. The arterial blood pressure in the rabbit was somewhat low on the second, fourth and eighth day after the ligation, but otherwise

normal. We conclude that we fail to find in rabbits any data that support the shock-theory after SRVCL. Other experiments also support this (38). Nor were the adrenal lesions (paper V) preponderant amongst the succumbing animals.

Another theory is that the adrenals are suffering from stasis after SRVCL, and their inefficiency would lead to shock (60). If so, a substitution of corticosteroids would help. Nobody has been able to show that, and further thoracic caval constriction even leads to increased liberation of adrenal hormones (22, 28).

In our experiments with adrenalectomy (paper III), the biochemical effects were quite different from SRVCL and nephrectomy. Only a slight steady hyperkalaemia was found. The high mortality of 50 % after 48 hours is a well-known consequence as no substitution, not even with saline, was given. We can conclude that neither the experience from literature nor our experiments support the suggestion that SRVCL leads to adrenal inefficiency.

The third theory is that the animals die in acute uremia. Against this argues that the animals die so quickly, often within the three first days. Some facts argue for uremia. Many authors, including us, have found oliguria-anuria, proteinuria, and sometimes hematuria after SRVCL (2, 16, 17, 45, 55).

It is also well known that both patients and animals get raised creatinine and BUN after SRVCL (8, 33, 36, 59, 71). We (paper I) found not only oliguria, low excretion of Urea-N, low urine osmolality, and high protein leakage, during the first postoperative day, especially pronounced in those rats that later died; but we also found that the mortality was much higher in the older animals and that the younger ones died earlier - within the first three postoperative days - whereas the period in the older ones covered the whole postoperative week. Similar mortality pattern is seen in rats after nephrectomy (10). This is not a proof but an indication that some rats die in an acute uremia. In paper II, we demonstrate that the animals had a dramatic rise of potassium after SRVCL (Fig. 1), with a maximum already after 12 - 15 hours postoperatively. Values up to 10 mE/l are seen. Probably higher potassium values exist but those animals die and are lost from the study. We consider that this hyperpotassaemia is the cause of early death after SRVCL.

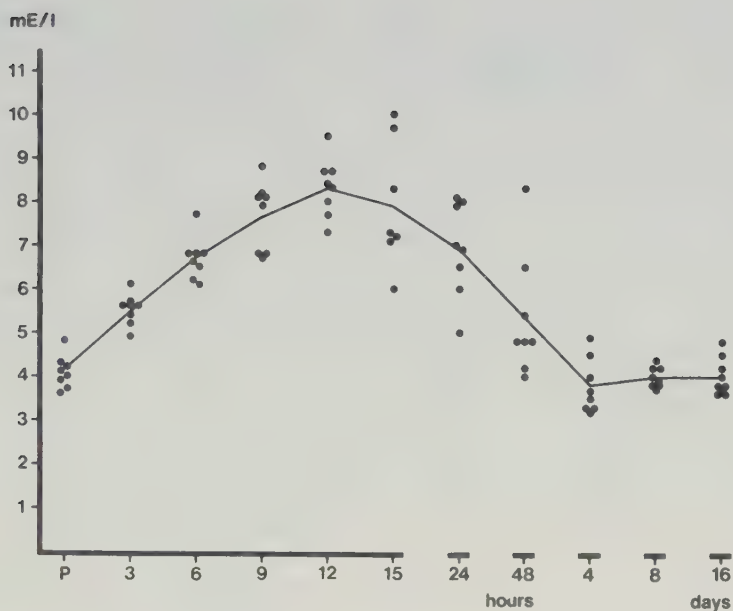


Fig. 1. Potassium in serum after SRVCL.

Nobody has ever shown this hyperpotassaemia before, but Siga (68) found on dogs a sharp and high T-wave after SRVCL, which can be caused by a high potassium value. Unfortunately he did not measure potassium, but on a dog after an oblique interrenal vena cava ligation, he found elevated potassium values after 24 hours which increased, and the dog died the following day. Siga's study supports the contention that the same cause of death after SRVCL exists for dogs as for rats. The surviving human case reported by Vasko (73) also showed a slight hyperkalaemia.

It can seem a mystery that the potassium is rising so fast, but also after nephrectomy (paper III) we found an early hyperkalaemia with maximum at the same time (Fig. 2). Although the potassium curve after nephrectomy appeared to be biphasic with a mini-

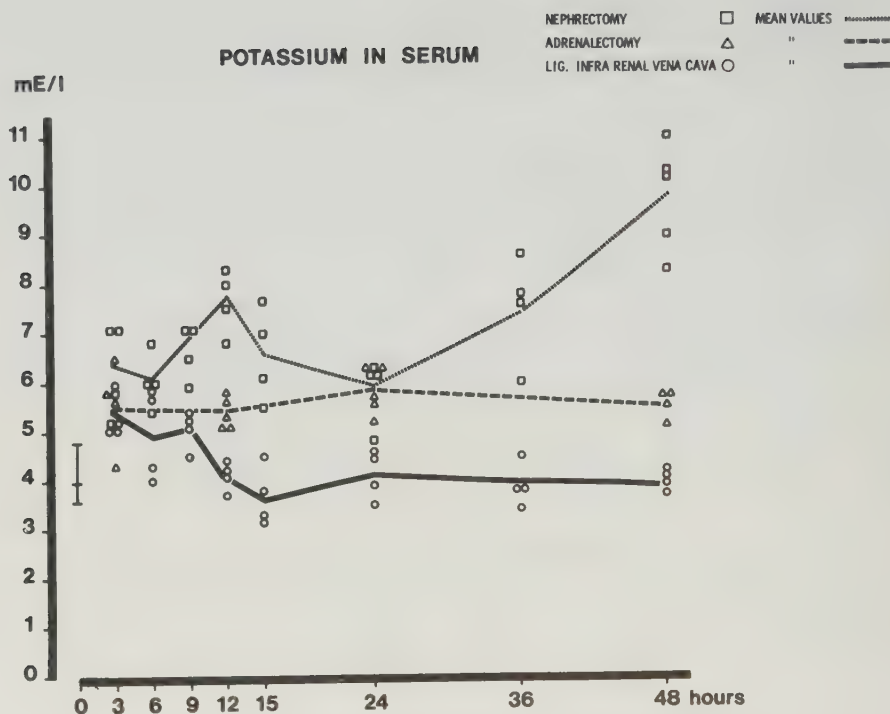


Fig. 2.

Potassium in serum after nephrectomy, adrenalectomy and IRVCL.

mum 24 hours after SRVCL; thereafter, we got a linear rise.

We consider that this early synchronous hyperpotassaemia after SRVCL and nephrectomy can have some connexion, although the potassium after SRVCL is higher; but here we have not only an acute renal failure, but also the lower part of the body stasied by the ligature. There are data that favour the idea that different organs can have different membrane potentials with altered shift over the cell membranes (31,72,76). Thus the potassium and hyd-

rogen concentrations can vary between organs. The slight hyperkalaemia seen during the first 9 hours after IRVCL, can give an idea of how much the stasis in the extremities can contribute to serum potassium after SRVCL. In paper VI, we not only confirm this, but make clear that the kidneys are the great losers of potassium if we accept presented facts that rubidium both physically and physiologically, resembles potassium (57,34). Rubidium is accumulated intracellularly in preference to K, obviously owing to several factors (3,4,57,70). But added to that, it is also more strongly cell-bound than potassium (61), and tissue concentration similar to potassium is highly pH dependent (61,62). As the half life of ^{86}Rb is 19 days compared with ^{43}K , 12 hours, and also easy to estimate, we found it rather ideal as a substitute for potassium.

Williams et al (76) measured membrane potentials and extra- and intracellular electrolytes 24 hours after nephrectomy but we fail to find the facts in his article that explain the behaviour of serum potassium after nephrectomy that we have shown.

It seems curious that nobody before has found this biphasic potassium curve. Several authors have studied potassium after nephrectomy or ureter ligation (37,65,72,35) also on rat (4,15,18). As nobody has expected anything other than a linear rise of potassium, as well as urea and creatinine, the parameters have not been measured often enough to reveal our interesting findings. Thysell (72), however, showed a faster potassium rise during the first 12 hours after nephrectomy. Often the first postoperative samples are taken after 24 hours, i.e. when we found relatively low potassium values in serum after nephrectomy.

In any discussion of potassium, the pH must always be born in mind. The slight acidosis seen after SRVCL (paper II) in the general circulation can only be responsible for a minor part of the hyperpotassemia; this is also supported by the earlier-mentioned findings after IRVCL.

Probably the acidosis in the stased part of the body is much more pronounced locally than is evident from the figures of pH and lactate in the general circulation.

24 hours after nephrectomy we see relatively low potassium values; also after SRVCL at that time, the potassium values are somewhat low together with a normal pH after nephrectomy and SRVCL — except one value. Although on the first day after SRVCL, the potassium is considerable higher than after nephrectomy, the difference is not fully significant. SRVCL but not nephrectomy gives a mortality the first day, due to hyperkalaemia we think. Thus we cannot catch the highest potassium values after SRVCL. This opinion is supported by the morphological findings (paper V) where the most conspicuous lesions — medullary infarctions — were found in the succumbing and in the oldest rats.

Medullary localization of the renal lesions after advanced venous stasis is also reported by others (21,11,67). The blood congestion is most pronounced in this part of the kidney, but an altered intrarenal blood flow distribution can also contribute (39,50).

Other organs in many ways control the kidneys. Possibly, the kidneys also influence some organs or parts of their functions, e.g. membrane pump. After manipulations with the kidneys such a system can come out of balance and can lead to metabolic changes as shown here. As only about 2 % of the total body potassium is extracellular, already minor, especially acute, changes in the intracellular pool can give high deviations in serum, especially when the kidneys are lacking or non-functioning.

Creatinine 24 hours after SRVCL had a mean of 4 mg % compared with 4.5 mg % after nephrectomy, 48 hours after SRVCL, isolated values up to 7 mg % were seen, which is very close to those creatinine values measured at the same time after nephrectomy.

Those data give a good picture of the grade of the acute renal failure after SRVCL.

Urea in serum behaved quite differently, but the origin is also different from that of creatinine. 24 hours after SRVCL, urea concentration in serum had a mean of 75 mmol/l, which corresponds to 210 mg % urea-N. 24 hours after nephrectomy, only 130 mg % urea-N was measured in serum and after 48 hours about 300 mg % compared with 80 mmol/l urea after SRVCL at the same time. We interpret this data to mean that the first day after SRVCL there is much greater tissue damage than after nephrectomy mirrored in the higher urea 24 hours after the operative procedures. The morphological findings in paper V support this hypothesis. 24 hours later, the kidneys that have been exposed to SRVCL either are coming into function again

or the animals are dead or dying in an acute renal failure. It cannot be denied that the relatively low urea-N 24 hours after nephrectomy has a connexion with the low potassium values at the same time.

In the first three papers, we present strong evidence that the cause of death after SRVCL is hyperkalaemia combined with acute renal failure. In the fourth work, we also give a quantitative idea of the renal insufficiency. Moreover, we exclude the shock theories as cause of death, at least in relatively young and healthy rabbits.

Older animals are probably more sensitive to a fall in blood pressure, as is seen in humans after IRVCL for thrombosis (5). Their collaterals are probably also more difficult to stimulate. Also in dogs, IRVCL can have a deleterious outcome (20).

We found (paper IV) that the renal vein pressure (Fig. 3) increased about fourfold immediately after the acute suprarenal occlusion, and the cardiac output fell about 30 - 40 %, but the renal blood flow fell immediately more than 50 %. Whereas almost normal cardiac output could be seen already after 2 - 4 days, the renal blood flow required much more time to reach the normal level. This indicates that the highly increased renal vein pressure plays a highly important role in the induction of acute renal failure. (Fig. 4).

This supposition is confirmed by the very low extraction of ^{51}Cr -EDTA (Fig. 5) and ^{125}I -Hippuran (Fig. 6) four and eight days after the SRVCL when the renal blood flow was good while the renal vein pressure still was elevated. Those animals that appeared to have the lowest extraction of the isotopes on the fourth day and on the eighth day after SRVCL also died spontaneously the day after the investigation; they were bony and marked by the renal insufficiency. We found that the main drainage from the kidneys was rapidly established via the suprarenolumbar veins, which successively increased in size. The vena cava (Fig. 7) on the other hand, diminished in size successively caudal to the renal vein, and there was a segmental drainage from it through ileolumbar and lumbar veins. We have not seen this described earlier, and our findings make it clear that, in visualizing the vena cava by roentgen contrast after an occlusion, it is necessary to use a catheter technique. Whereas we found that normalization of renal venous pressure was nearly

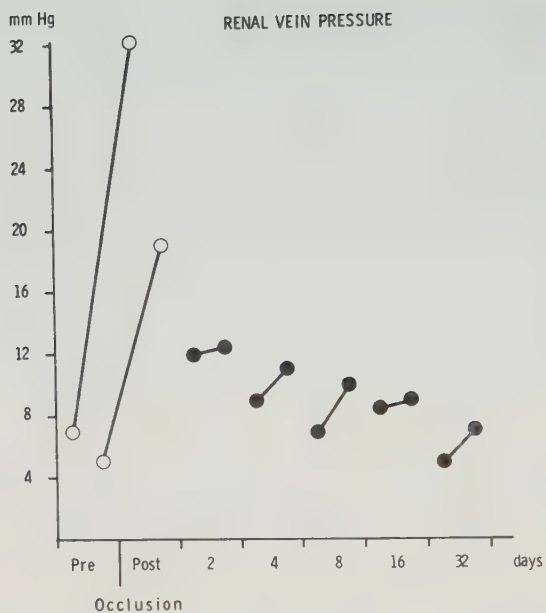


Fig. 3. Renal vein pressure.

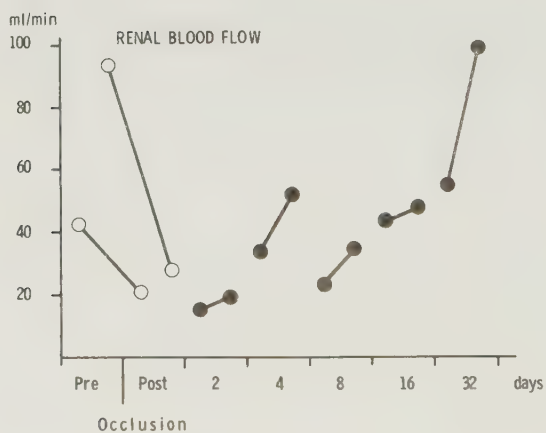


Fig. 4. Renal blood flow.

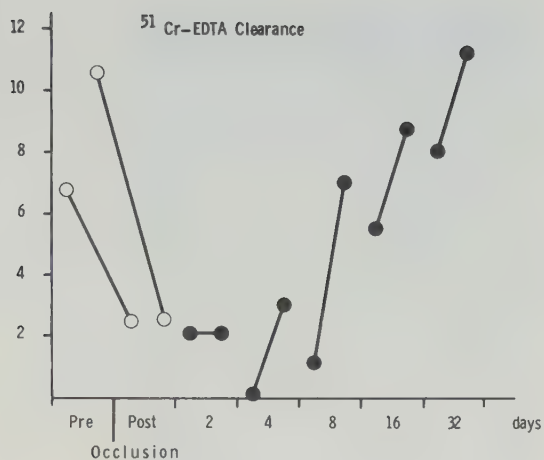


Fig. 5. EDTA-extraction.

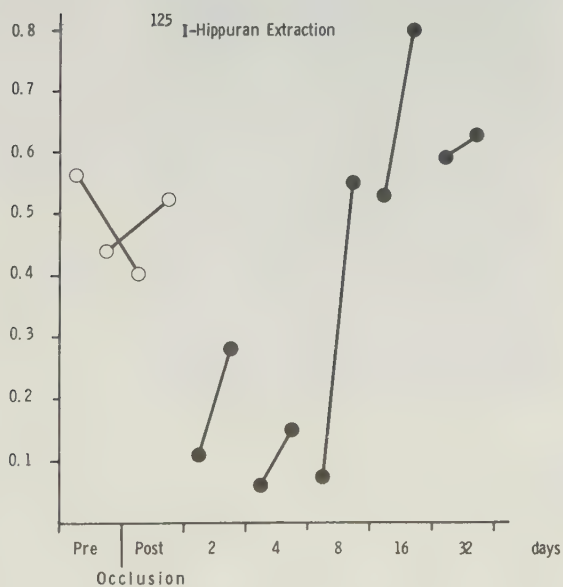


Fig. 6. Hippuran extraction.

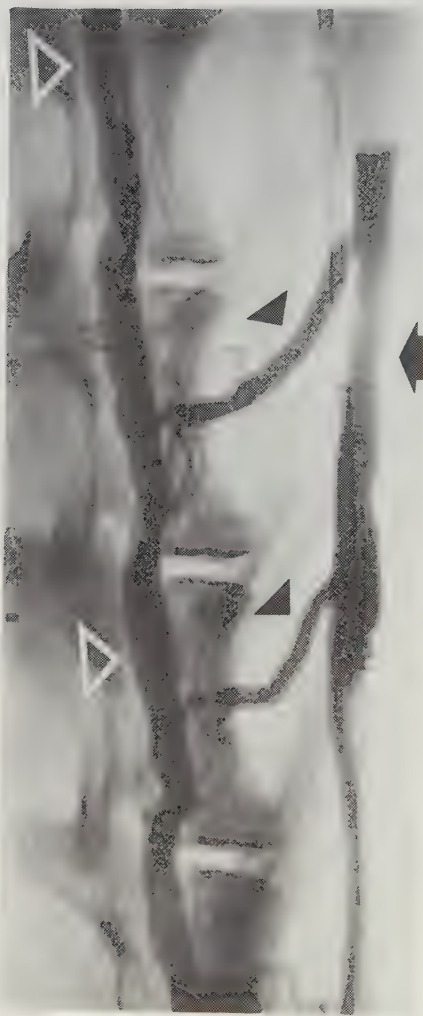


Fig. 7.

Cavography. Lateral projection. Four days after the ligation of the inferior caval vein. The injection of contrast medium was made by a catheter in the lower part of the caval vein (▲) . Segmental drainage via lumbar veins (▲) to the vertebral veins (△) .

won after 32 days, Narkiewicz (48) found normal pressure already after one week in cat. Other authors have confirmed that normal venous pressure is achieved first after a considerably longer time (36).

Conclusions

1. SRVCL induces a cessation of urine production for one day, a short proteinuria and concentration defects for some weeks for the survivors, especially pronounced in older rats.
2. SRVCL induces a dramatically fast rise of potassium with maximum after 12 - 15 hours combined with an acute renal failure. Rats succumbing after SRVCL die early in hyperkalaemia or somewhat later in a uremia.
3. Nephrectomy in rats causes a biphasical rise of potassium with its first maximum after 12 hours. Whereas adrenalectomy causes a slight but constant hyperkalaemia and IRVCL only a slight hyperkalaemia for 9 hours.
4. SRVCL does not cause a shock-state in rabbits, but an acute renal failure, most pronounced on the fourth day. Normal extraction of EDTA and Hippuran have been measured after eight days. The function of glomeruli seemed to be more affected than the function of the tubuli.
5. The acute morphological renal lesions after SRVCL are necrosis and degeneration of tubules, most conspicuous in the inner stripe of the outer medulla and the adjacent inner medulla. Medullary congestion was advanced, whereas the glomerular changes were minimum. The most extensive lesions, even medullary infarcts, were found in succumbing animals. The late morphological sequelae were minimum.
6. Mainly the kidneys, but to some extent also the thigh musculature, contribute to the early hyperkalaemia after SRVCL.

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